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# Study on antibody-conjugated drugs and targeted therapy for triple-negative breast cancer

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**Abstract.** Statistics show that, second only to lung cancer, breast cancer is now the most common type of cancer worldwide. Compared to other forms of breast cancer, triple negative breast cancer (TNBC) has a worse prognosis, extensive metastases, and poor efficacy, making treatment more difficult. antibody-drug conjugates (ADCs), have become a hot topic in targeted tumor therapy research. Gosa tuzumab is the first drug approved for advanced TNBC treatment globally. However, challenges remain in the clinical use of ADCs, such as limited delivery of ADCs to target cells and suboptimal anti-tumor effects. This article analyzes targeted therapy methods and ADCs for TNBC, summarizes current market gosa tuzumab and ongoing clinical trials for ADCs drugs, providing a reference for further study on TNBC treatment with ADCs. Nevertheless, issues like drug resistance, adverse reactions and combination strategies with other chemotherapy inhibitors for TNBC treatment warrant further investigation in future clinical trials.

**Keywords:** Antibody-conjugated drugs, targeted therapy, triple-negative breast cancer.

## 1. Introduction

According to statistics from the International Cancer Research, it is projected that in 2020, there will be over 2.3 million new cases of breast cancer worldwide, making it the second most common cancer after lung cancer. Approximately 90% of these cases occur in biological women, posing a serious threat to human health [1]. Breast cancer can be classified into four main types: Luminal A, Luminal B, HER2-positive, and TNBC. TNBC is characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2) expression as determined by immunohistochemical examination [2]. TNBC is highly aggressive with a poor prognosis and tends to metastasize distantly [3]. The etiology of TNBC remains unclear; however, factors such as age, endocrine status, and family history are considered risk factors for its development. Due to high tumor mutation rates and challenges in studying disease mechanisms, TNBC is more difficult to treat compared to other subtypes of breast cancer.

There are currently five classes of drugs used for treating TNBC. The first class consists of chemotherapy drugs which serve as the cornerstone treatment for TNBC; however they often come with significant side effects due to their cell cycle-specific anti-tumor properties. The second class includes immunotherapy drugs like cyclophosphamide injection which work by enhancing the body's immune

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function to eliminate cancer cells. Aromatase inhibitors make up the third class - an example being letrozole tablets - which block estrogen synthesis through inhibition of aromatase activity and are suitable for postmenopausal breast cancer patients. Sensitizing agents form the fourth class aimed at increasing tumor cell sensitivity towards therapeutic drugs in order to enhance treatment efficacy; an example being gold nanoparticles. Lastly, monoclonal antibody drugs such as Bevacizumab injection constitute the fifth class - these targeted therapies can precisely reach lesion sites thereby improving drug effectiveness and utilization rate [4].

## 2. ADCs and their mechanism of action

Currently, immunotherapy and chemotherapy are the most commonly used treatments for TNBC. However, due to the poor prognosis of TNBC patients, these two therapies have shown obvious side effects and drug resistance. In recent years, ADCs as a new type of anti-tumor drugs, have become a hot spot in the study of tumor targeted therapy. ADCs consists of three parts: monoclonal antibodies with tumor antigen specificity, cytotoxic drugs with strong killing power, and stable lytic or non-lytic linkers [1]. The mechanism of action is that ADCs uses monoclonal antibody as the carrier to recognize the surface antigen of tumor cells, and cytotoxic drugs as the “warhead”. The two can target tumor cells through linker coupling, but are almost non-toxic to normal cells, and accumulate cytotoxic drugs on the surface of tumor cells, playing a high-efficiency and low-toxicity role. ADCs bind to antigen-positive tumor cell targets, and then endocytosis into tumor cell lysosomes mediated by receptors to form early endosomes containing ADC-antigen complexes. Through a series of mechanisms, lysosomes create a low-pH environment that promotes the cleavage of ADCs and the release of toxic substances, and then cytotoxic drugs cause cell death in a variety of ways, such as DNA insertion into RNA or inhibition of microtubule polymerization. ADCs can also mediate tumor cell death by entering neighboring tumor cells through the “bystander effect” or by destroying the matrix surrounding the tumor, depending on the various effects mediated by ADCs, including CDC, ADCC, or ADCP triggering immune effector cells to release cytotoxic drugs within tumor cells, thereby inducing tumor cell death. In addition, when the targeted tumor cell surface specific antigen is a molecule involved in tumor cell growth, differentiation, proliferation, metastasis and other signal transduction, the combination of MAB with the post blocks its downstream signal transduction pathway and can also inhibit the proliferation of tumor cells [5].

## 3. Pharmaceutical analysis

### *3.1. Bevacizumab*

According to research, bevacizumab has a relatively high proportion of application in first-, second-, and third-line treatments. Its treatment scope covers a variety of malignant tumors, and is clinically more effective than other drugs offer significant advantages [6]. Bevacizumab mainly exerts anti-tumor effects as a vascular endothelial growth factor (VEGF) antagonist. It specifically binds and inhibits VEGF, preventing it from binding to receptors on endothelial cells, thereby hindering the formation of new blood vessels. During tumor growth, solid tumors rely heavily on vascularization to meet their high metabolic needs, obtain nutrients and oxygen, and excrete metabolic waste products [7]. Among the angiogenic factors secreted by tumors, VEGF, especially VEGF-A, is a key factor in inducing tumor angiogenesis. VEGF activates VEGF signaling in endothelial cells by binding to VEGF receptor tyrosine kinases (VEGFR1-3), stimulating the proliferation and survival of endothelial cells while enhancing vascular permeability to meet the metabolic needs of tumor growth.

As a result, bevacizumab significantly reduces the proliferation and spread of malignant cells. Bevacizumab significantly improved overall survival, progression-free survival, and response rate when used in conjunction with other treatments as opposed to chemotherapy alone (all $P < 0.05$). However, new research has cast doubt on bevacizumab’s ability to successfully stop the growth of tumor cells; as a result, bevacizumab is mostly employed in clinical settings in conjunction with other chemotherapeutic

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medications. Statistics from Zhejiang Cancer Hospital show that over 90% of bevacizumab treatments need the use of additional chemotherapy medications, as shown in the table 1.

**Table 1.** Bevacizumab treatment regimen [7].

| Therapeutic regimen | Frequency | Consitituent ratio(%) |
|---|---|---|
| Single-used scheme | | |
| Bevacizumab alone | 35 | 9.16 |
| Co-use scheme | | |
| In combination with platinum drugs | 63 | 16.50 |
| In combination with yew containing drugs | 69 | 18.05 |
| In combination with anthracycline-containing drugs | | |
| In combination with antimetabolic drugs (ex. Chlorouracil) | 193 | 50.54 |
| In combination with other chemotherapeutic agents | 16 | 4.18 |
| In combination with targeted therapeutic agents | 1 | 0.26 |
| Total | 382 | 100 |

### *3.2. Gosa Tuzumab (SG)*

SG is the first ADC to be globally approved for the treatment of advanced TNBC. As the inaugural ADC targeting Trop-2, SG received accelerated approval from the U.S. Food and Drug Administration (FDA) in 2020. It was subsequently approved in 2021, for the treatment of patients with locally advanced or metastatic TNBC who had undergone at least two prior treatment regimens, including at least one for metastatic disease. For patients with locally advanced or metastatic urothelial carcinoma (UC) who have previously had treatment with platinum-based chemotherapy and a programmed death receptor and its ligand 1 (PD-1/PD-L) inhibitor. Adult patients with locally advanced or metastatic TNBC who had received at least two prior systemic therapies, including at least one for metastatic cancer, were eligible to receive SG as of June, 2022, in China. SG is comprised of a cleavable linker, an active metabolite of irinotecan called SN-38, and a monoclonal antibody called hRS7 that targets trophoblast cell surface antigen 2 [8].

Membrane glycoprotein TROP-2 is overexpressed in breast, colorectal, and urothelial carcinomas, among other epithelial cancers. It plays a role in cellular activities like migration and proliferation [8]. With a high drug-to-antibody ratio of 7.6:1, hRS7, as a carrier, maintains high stability in the bloodstream, delivering a high concentration of SN-38 to the tumor tissue. The antibody of SG specifically binds to TROP-2 on the surface of tumor cells, facilitating the internalization of SN-38 through phagocytosis [8]. SN-38, a topoisomerase inhibitor, is 20–136 times more potent than the parent compound irinotecan in xenograft tumor models, inducing DNA double-strand breaks and apoptosis [8]. Due to its pH-dependent linker, SG can directly hydrolyze and release SN-38 within the tumor microenvironment. This property allows SG to exert a direct cytotoxic effect on tumor cells with low or no expression of TROP-2, independent of antibody-mediated targeting. This phenomenon is known as the ADC bystander effect [8].

In patients with TNBC who have progressed after multiple lines of treatment, including taxanes, anthracyclines, platinum-based agents, immunotherapy, and poly ADP-ribose polymerase (PARP) inhibitors, SG continues to demonstrate significant efficacy [8]. This has shifted the paradigm for the treatment of advanced TNBC, which was predominantly reliant on single-agent chemotherapy.

### *3.3. Other Medications*

#### *3.3.1. Datopotamab Deruxtecan (Dato-DXd, DS-1062a)*

Datopotamab deruxtecan is a therapeutic agent that incorporates a DNA topoisomerase I inhibitor, DXd. It demonstrates a high degree of specificity for TROP2, a target antigen that is abundantly expressed in

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epithelial tumors. This targeted approach is designed to maximize the drug's impact on cancer cells while minimizing its effects on healthy cells [9]. Upon binding to TROP2 on the surface of tumor cells, Dato-DXd is internalized through endocytosis. Once inside the cell, it is processed through the cellular transport system and ultimately delivered to the lysosome. The acidic environment within the lysosome facilitates the release and activation of DXd [10]. Once activated, DXd initiates its therapeutic action by inducing DNA damage and apoptosis in the tumor cells, thereby contributing to tumor shrinkage and preventing its metastasis. This mechanism is pivotal to its anti-cancer efficacy [9]. Although Dato-DXd is currently in Phase III clinical trials, new medications like this may still present unforeseen risks and side effects when widely adopted, necessitating ongoing market evaluation and surveillance.

### *3.3.2. Pembrolizumab*

Originally developed as a monoclonal antibody for melanoma treatment, pembrolizumab (Keytruda) has expanded its therapeutic scope. On November 9, 2022, Merck announced that pembrolizumab has received approval from the National Medical Products Administration (NMPA) of China for use in combination with chemotherapy as a neoadjuvant treatment. Following surgery, it is also used as a standalone adjuvant therapy to further enhance treatment outcomes [11]. PD-1, a protein predominantly expressed on the surface of activated immune cells such as T cells, B cells, and macrophages, plays a crucial role in immune regulation. When tumor cells express high levels of PD-L1, they can bind to PD-1 on immune cells, leading to immune evasion and shielding the tumor from immune attack. Pembrolizumab, a PD-1 immune checkpoint inhibitor (ICI), counters this by blocking the CTLA-4 or PD-1/PD-L1 pathways, thereby reactivating the immune system's ability to target and eliminate tumor cells, effectively suppressing tumor growth and metastasis [12]. It is particularly beneficial for the treatment of early-stage, high-risk TNBC patients whose tumors have been confirmed to express PD-L1 through validated testing methods.

Recent studies have demonstrated that the combination of pembrolizumab with taxane and anthracycline-based chemotherapy significantly elevates the pathological complete response rate to 44%, a substantial improvement over the 17% rate observed with chemotherapy alone. This synergistic effect is especially pronounced in patients with early-stage, high-risk TNBC, where the pCR rate has been shown to increase from 22% to 60%. Furthermore, patients achieving pCR with pembrolizumab have demonstrated significantly improved long-term survival outcomes, with a 3-year event-free survival rate reaching as high as 93% [13]. These findings underscore the potential of combining anthracycline-based chemotherapy with PD-1/PD-L1 inhibitors during the neoadjuvant phase to not only increase the likelihood of pCR in TNBC patients but also to significantly enhance their long-term prognosis.

### *3.4. Drug Comparison*

In summary, these four drugs each possess unique characteristics and are targeted towards different types of cancers and patient populations. When utilizing these medications, it is imperative to select the appropriate drug based on the specific conditions of the patient and the characteristics of the disease, and to strictly adhere to medical guidance and medication protocols.

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**Table 2**. Comparison of selected TNBC ADC drugs

| Drug Name | Target | Mechanism of Action | Treatment Regimen |
|---|---|---|---|
| Bevacizumab | VEGF receptor | Inhibits tumor cell growth indirectly by suppressing the formation of new blood vessels. | Used in combination with other chemotherapy drugs. |
| SG (Trodelvy) | Trop-2 | Undergoes receptor-mediated endocytosis, entering tumor cells where it is degraded by lysosomes to release its payload, exerting cytotoxic effects. Additionally, SG possesses antibody-dependent cellular cytotoxicity (ADCC) and signaling inhibition effects, collectively contributing to its antitumor efficacy. | Used in combination with other inhibitors. |
| Datopotamab Deruxtecan | Trop-2 | Binds to TROP-2 on the surface of tumor cells via a humanized anti-TROP2 IgG1 monoclonal antibody. The linker hydrolyzes to release the toxin, which inhibits DNA topoisomerase I, causing DNA single-strand breaks and inducing DNA damage and tumor cell death. | Not yet widely used in clinical practice, and treatment regimens are still under discussion. |
| Pembrolizumab | PD-1 | By binding to PD-1/PD-L1, pembrolizumab blocks the PD-1/PD-L1 signaling pathway, allowing immune cells to recognize and attack tumor cells. Additionally, pembrolizumab promotes antigen presentation, enhancing the effector function of antigen-specific cytotoxic T cells. | Combined with chemotherapy as a neoadjuvant treatment approach, and used alone as adjuvant treatment post-surgery. |

Other Therapeutic Directions (Table 2). Current innovative approaches to treating TNBC can be categorized into four main areas: targeted therapy, immunotherapy, gene editing technology, and cell therapy.

For targeted therapy, identifying targets within TNBC is fundamental. PARP plays a role in DNA repair within tumor cells, and PARP inhibitors have demonstrated antitumor activity against TNBC, particularly in tumors with BRCA1 and BRCA2 mutations. This suggests their potential as targets. PARP inhibitors currently under development include Olaparib, Veliparib, and Iniparib. These drugs have shown certain antitumor activities in in vitro experiments, animal studies, and phases I and II clinical trials. However, their long-term efficacy and issues of drug resistance in the treatment of TNBC still require further investigation [14].

In the realm of immunotherapy, ICIs are commonly used. PD-1 is a crucial immunosuppressive molecule, and immune modulation targeting PD-1 holds significant importance in combating tumors, infections, autoimmune diseases, and in the context of organ transplants. The interaction between PD-1 and its ligand, PD-L1, on the surface of tumor cells can lead to the persistent activation of the PD-1 pathway, resulting in the suppression of T cell function and their inability to eliminate tumor cells, thus facilitating immune evasion by tumor cells [15]. Consequently, PD-1/PD-L1 inhibitors can be employed for the immunotherapy of TNBC.

Additionally, gene editing technology has made certain advancements. Research has found that COP1 plays a critical role in the development and spread of tumors. COP1 regulates the protein levels of the transcription factor C/ebpδ through the adapter protein Trib2, and C/ebpδ can inhibit the release

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of macrophage chelators by cancer cells. In TNBC, the suppression of COP1 leads to a decrease in macrophage infiltration and an increase in sensitivity to anti-PD-1 therapy [16]. In mouse models, the knockout of COP1 significantly inhibited tumor growth and extended the survival time of mice, particularly in those treated with immune checkpoint blockade (ICB) [16].

Lastly, research on tumor stem cells provides robust evidence for cell therapy. ALDH+ cells, due to their high self-renewal capacity and multilineage differentiation potential, are considered key contributors to therapy resistance and recurrence in breast cancer. A research team discovered that KK-LC-1 (Kita-Kyushu Lung Cancer Antigen-1) is highly expressed in TNBC ALDH+ cells and promotes its ubiquitination and degradation by binding to FAT1, thereby affecting the Hippo signaling pathway. This leads to the nuclear translocation of the transcription factors YAP1 and ALDH1A1, enhancing the stemness of ALDH+ cells. To reverse the malignant characteristics induced by KK-LC-1 expression, researchers have identified a small molecule inhibitor named Z8 using computational methods. This compound can disrupt the binding between KK-LC-1 and FAT1, thereby reactivating the Hippo pathway. The activation of this mechanism reduces the stemness and vitality of TNBC ALDH+ cells, suppressing tumor growth and metastasis.

## 4. Conclusion

ADCs are currently a primary direction in the treatment of TNBC, primarily delivering small molecule drugs to tumor cells via VEGF receptors, Trop-2 receptors, and PD-1, thereby exerting their tumor-killing effects. In the treatment of TNBC, ADCs offer significant advantages, such as high selectivity, high efficiency, and low side effects. However, despite certain successes in the development and application of ADCs, there are still some drawbacks and challenges. The preparation process of ADCs is complex, involving multiple steps and delicate operations, which increases production costs and technical difficulty. The efficacy of ADCs is influenced by various factors, such as tumor cell heterogeneity, antigen expression levels, drug dosage, and treatment duration. This article only analyzes a portion of the drugs used for treating TNBC, which may have some limitations. With the continuous advancement of technology and in-depth clinical research, it is believed that more innovative ADCs will emerge in the future, providing more effective and safe options for tumor treatment. At the same time, research on the preparation process, stability, efficacy, and safety of ADCs will continue to deepen, promoting the application and development of ADCs in the field of tumor therapy.

## Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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